

**PATENT**

Attorney Docket No. 225326  
Client Reference No. 153,098US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

Bentolila et al.

Art Unit: Unassigned

Application No. Unassigned

Examiner: Unassigned

Filed: November 24, 2003

For: MODAFINIL FORMULATIONS

**CLAIM OF PRIORITY**

Mail Stop Patent Application  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

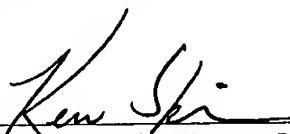
Dear Sir:

In accordance with the provisions of 35 USC 119, Applicants claim the priority of the following application:

Application No. 153,098, filed in Israel on November 26, 2002.

A Certified copy of the above-listed priority document is enclosed.

Respectfully submitted,



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מדינת ישראל  
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משרד המשפטים  
לשכת הפטנטים

This is to certify that annexed hereto is a true copy of the documents as originally deposited with the patent application of which particulars are specified on the first page of the annex.

זאת לתעודה כי רצופים בהזה העתקים נכונים של המסמכים שהופקדו לראשונה עם הבקשה לפטנט לפני הפרטיהם הרשומים בעמוד הראשון של הנספה.

This 13-10-2003 חיון

לשייל והבוחנים  
רשות הפטנטים

Commissioner of Patents



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**בקשה לפטנט**

Application for Patent

מספר: Number	153098
תאריך: Date	26-11-2002
הוקרטס. הדחה Ante/Post-dated	

(אני, (שם המבקש, מענו — ולגביו גוף מאוגן — מקום התאגדותו)  
(Name and address of applicant, and, in case of a body corporate, place of incorporation)

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שםו הוא  
Owner, by virtue of

הדין  
the Right of Law

בעל אמצעאה מכון  
of an invention, the title of which is:

תכשירי רוקחות המכילים מודאפינייל

בעברית  
(Hebrew)

PHARMACEUTICAL COMPOSITIONS CONTAINING MODAFINIL

(באנגלית)  
English

מבקש בזאת כי ינתן לי עליה פטנט.

*בקשת חלוקה Application for Division	*בקשת פטנט נוסף Application for Patent of Addition	דרישת דין קיימה Priority Claim		
מבקש פטנט from Application No. _____ Date _____	לבקשתה/לפטנט to Patent/Appn. No. _____ Date _____	מספר/ סימן Number/Mark	תאריך Date	מדינת האגודה Convention Country
ימי נח: כללית – עד יונש P. O. A.: general – to follow				
הונש בעין Has been filed in 99756				
המען למסירת החותם ומסמכים בישראל Address for Service in Israel				
WOLFF, BREGMAN AND GOLLER P. O. Box 1352 Jerusalem, Israel, 91013 וולף, ברגמן וגולד ת.ד. 1352 ירושלים				
חתימת המבקש Signature of Applicant				
WOLFF, BREGMAN AND GOLLER by: <i>A. Gold</i>				
				לשימוש הלשכה For Office Use

**PHARMACEUTICAL COMPOSITIONS CONTAINING MODAFINIL**

**תכשירי רוקחות המכילים מודאפיניל**

The present invention relates to a safe and effective oral composition of modafinil. This composition is characterized by the large size of the particles of modafinil utilized therein.

Modafinil whose chemical name is 2-[(diphenylmethyl)sulfinyl]acetamide, is marketed in various countries under several brand names such as Provigil®, Modiodal® and Vigil®. It is sold as tablets containing 100 (and in some countries also 200) milligrams of modafinil. This drug is used in treating conditions of hypersomnia and narcolepsy, or in other words, it is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.

US patent number 5,618,845 (assigned to Cephalon Inc.) teaches the significance of the particle size distribution (abbreviated henceforth as PSD) of modafinil in its pharmaceutical use. Early safety studies of modafinil tablets, done on healthy human volunteers, did not show any adverse effect on humans in doses up to 4500 milligrams. However, in clinical trials conducted later in the US, serious adverse effects such as elevation of heart rate and increase in the blood pressure were observed in some volunteers at doses of 800 milligrams. Further investigation showed that tablets made with the "late" material had faster dissolution profile than tablets made from "early" material. Tests done on dogs also showed that tablets prepared from the "late" material had higher blood levels than those made from the "early" material.

In the patent it is stated that the reason for these differences between the early study, done out of the United States, and the new study, conducted in the United States, is the difference in the PSD of the material used to formulate the tablets.

The "early" batches (data for 4 batches was reported) contained modafinil particles having a median value of 94-143 $\mu$ , and 95% of the particles were smaller than 220-280 $\mu$ . The "late" batches (data for 2 batches was reported) had a median value of 31-50 $\mu$  and the 95% of the particles were smaller than 110-150 $\mu$ .

Based on these findings US 5,618,845 claims:

- "A pharmaceutical composition comprising a substantial homogeneous mixture of modafinil particles wherein at least about 95% of the cumulative total of modafinil particles have a diameter of less than about 200 $\mu$ ."
- "The composition" stated above "wherein said particles have a median diameter of between about 2 $\mu$  and about 60 $\mu$ ".

The term "about" used for the percentage of the crystals and for their size is defined there as  $\pm 10\%$  of the given value.

This patent teaches that the PSD of the modafinil in the tablet plays an important role on its therapeutical effect. The "early" and the "late" products differ in:

- Dissolution rate (in vitro)
- Blood level profiles (in vivo)
- Occurrence of adverse effects

The differences are attributed to the different PSD of the modafinil used. It clearly differentiates between "early" material having larger particles and "late" material having smaller particles.

Strict adherence to the specification of the PSD in the "late" material was declared to be very important for the safety (demonstrated by lack of adverse effects) and effectiveness (shown by the blood levels and dissolution rate) of the modafinil tablets. Safety and effectiveness are the requirements for approval of drugs by the health authorities.

Such a strict requirement on the PSD of modafinil in the tablet is a heavy burden on the chemical producer. The exclusion of large particles (above

200 $\mu$ ) and the strict specification are liable to lead to rejection of a considerable number of modafinil batches.

Surprisingly and contrary to the teachings of US 5,618,845, it has now been found that safe and effective pharmaceutical compositions of modafinil can be made using much larger particles of modafinil. The formulation according to the present invention has a dissolution rate profile similar to that of marketed Provigil® tablets. This can be achieved by using appropriate formulations techniques. In these compositions modafinil, having particle size distribution values significantly above the values claimed in US 5,618,845, have been used and, at the same time, said compositions have been found to have similar dissolution rate profiles when compared to Provigil® tablets. Thus and contrary to the teachings of the prior art, the present invention enables the production of modafinil tablets that are safe and effective without the need to take special care of the PSD of the modafinil used to make these tablets.

Thus according to the present invention there is now provided a safe and effective modafinil oral composition wherein 5-50% of the modafinil particles have a diameter greater than 200 $\mu$ .

In preferred embodiments of the present invention at least about 5% of the cumulative total of modafinil particles have a diameter of more than about 250 $\mu$ :

In especially preferred embodiments of the present invention at least about 10% of the cumulative total of modafinil particles have a diameter of more than about 200 $\mu$ .

Preferably at least about 15% of the cumulative total of modafinil particles have a diameter of more than about 190 $\mu$ .

Especially preferred are compositions according to the present invention wherein the median value of modafinil particles is more than about 10 $\mu$  preferably more than 80 $\mu$ .

The term "about" in the above PSD characteristics has the meaning of  $\pm 20\%$  of the stated value for the percentage of particles and  $\pm 10\%$  of the stated value of the particle size.

The statistical terms "mean", "median" and "mode" are used here in the same meaning as stated in US 5,618,845. Mean refers to the sum of the size measurements of all measurable particles measured divided by the total number of the particles measured. The term median indicates that about 50% of all measurable particles measured have a particle size less than the defined median particle size value, and that about 50% of all measurable particles measured have a particle size greater than the defined median particle size value. The term mode indicates the most frequent occurring particle size value.

The meaning of the term "Particle Size Distribution" (PSD) is a rather complex issue. Its meaning is crystal clear when one has spherical particles. The results are unique and easy to explain. However, once the particles shape is less similar to spheres, the results are less clear. Different techniques, will give different results. Additionally, in many techniques, the raw data is mathematically manipulated by algorithms to give the PSD results. Different algorithms may also lead to different results.

It has now been found that the modafinil particles used in the present invention are larger than those claimed by the Cephalon patent regardless of the technique used. For that purpose we have measured the PSD of the modafinil used in the present invention by two different methods.

Modafinil PSD was measured in US 5,618,845 by using a Hiac/Royco machine. This machine uses a light obscuration technique for the PSD measurement. We repeated the measurements of the PSD on a Hiac/Royco machine and compared it with a different laser beam obscuration technique offered by the commonly used Malvern machine. Both methods use light obscuration as means to evaluate the PSD, but they work on different

principles. The results confirmed the validity of our PSD measurements. Both methods gave similar values. Both methods also gave PSD results that are far away from the scope of the values claimed by US 5,618,845. The following table summarizes the data. Values are reported in microns. The term  $D(v,0.5)$  denotes the diameter of the largest particle found in 50% of the particles sorted in increasing order. The other two terms refer to 85% and 95% of the particles. The terms mean, median and mode are used in their regular statistical meaning.

Batch	Method	mean	Median	mode	$D(v,0.5)$	$D(v,0.85)$	$D(v,0.95)$
A	Hiac	51	134	196	133	229	282
	Malvern		107		107	235	318
B	Hiac	40	104	148	103	194	265
	Malvern		85		85	215	293
C	Hiac	51	148	193	148	231	277
	Malvern		128		128	228	303

The high similarity between the dissolution rate of Provigil® tablets and the tablets made by our new invention is an excellent indication for their bioequivalence. The Physician Desk Reference states that "Absorption of PROVIGIL tablets is rapid, with peak plasma concentrations occurring at 2-4 hours. The bioavailability of PROVIGIL tablets is approximately equal to that of an aqueous suspension." Since the absorption of modafinil seems not to be a limiting factor, it is safe to assume that similar dissolution rates indicate similar blood levels (hence similar therapeutic effect) for both products.

While the invention will now be described in connection with certain preferred embodiments in the following examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following

examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

#### Example 1.

Modafinil tablets containing 200 mg of modafinil were prepared from the active ingredient batches having the following PSD. (values are in microns):

Batch	D(v,0.5)	D(v,0.85)	D(v,0.95)	Median
A	107	235	318	107
B	85	215	293	85
C	128	228	303	128
D	95	217	297	95

### Example 2

Dissolution rates were measured in 0.1N HCl for the tablets prepared from modafinil described in example 1 and for Provigil® tablets 200 mg. The table summarizes the results.

Time (min)	% dissolved	
	Example 1 tablets	Provigil® tablets
0	0	0
10	67	59
20	82	81
30	89	90
45	94	94
60	97	95
75	98	96

It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

**WHAT IS CLAIMED IS:**

1. A safe and effective modafinil oral composition wherein 5-50% of the modafinil particles have a diameter greater than 200 $\mu$ .
2. A modafinil composition as claimed in claim 1 wherein at least about 5% of the cumulative total of modafinil particles have a diameter of more than about 250 $\mu$ .
3. A modafinil composition as claimed in claim 1 further characterized by that at least about 10% of the cumulative total of modafinil particles have a diameter of more than 200 $\mu$ .
4. A modafinil composition as claimed in claim 1 further characterized by that at least about 15% of the cumulative total of modafinil particles have a diameter of more than about 190 $\mu$ .
5. A modafinil composition as claimed in claim 1 to 4 further characterized by that the median of the modafinil particles is greater than 10 $\mu$ .
6. A modafinil composition as claimed in claim 5 wherein the median of the modafinil particles is greater than about 80 $\mu$ .

For the Applicant

WOLFF, BREGMAN AND GOLLER

by: *G. Gold*